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Iodine-131 tositumomab (Bexxar(R)): radioimmunoconjugate therapy for indolent and transformed B-cell non-Hodgkin's lymphoma.

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Tositumomab is an immunoglobulin G murine monoclonal antibody that binds to the CD20 antigen on the surface of normal and malignant human B-cells. Tositumomab is linked covalently with iodine-131 to produce the radioimmunoconjugate iodine-131 tositumomab (Bexxar((R))). The iodine-131 tositumomab regimen was approved by the US Food and Drug Administration in June 2003 for the treatment of patients with CD20-positive follicular non-Hodgkin's lymphoma, both with and without transformation, whose disease is refractory to rituximab (Rituxan((R))) and has relapsed following chemotherapy. The dose-limiting toxicity of iodine-131 tositumomab is bone marrow suppression and resulting cytopenias. Unlike chemotherapy, the majority of nonhematologic adverse events associated with iodine-131 tositumomab are mild to moderate in nature and usually self limited. Iodine-131 tositumomab represents one of the most active single agents for the treatment of recurrent indolent and transformed B-cell non-Hodgkin's lymphoma, as demonstrated by several clinical trials summarized in this review. At the present time, the use of radioimmunoconjugate therapy is largely limited to patients with disease refractory to rituximab therapy and transformed disease not amenable to high-dose therapy and autologous stem cell support. Longer follow-up of ongoing clinical trials should provide reassurance as to safety and insights as to the additive stem cell toxicity from iodine-131 tositumomab administration. Studies are also addressing the role of iodine-131 tositumomab as a component of initial therapy for indolent non-Hodgkin's lymphoma and in additional histologies of non-Hodgkin's lymphoma.

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[89] The BEXXAR® Therapeutic Regimen (Tositumomab and Iodine I 131 Tositumomab) Produced Durable Complete Remissions in Heavily Pretreated Patients with Non-Hodgkin's Lymphoma (NHL), Rituximab-Relapsed/Refractory Disease, and Rituximab-Naive Disease. Session Type: Oral Session

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Introduction: The BEXXAR therapeutic regimen was recently approved for the treatment of patients with CD20-positive, follicular NHL, with and without transformation, whose disease is refractory to rituximab and who have relapsed following chemotherapy. Approval was based on a study that included 40 patients, 35 (88%) of whom met the definition of rituximab-refractory (no response or a duration of response of ≤ 6 months). The response rate for the entire population was 68%, with a median duration of response of 16 months. The results of this study were supported by demonstration of durable objective responses in 4 other studies enrolling 190 rituximab-naive patients with follicular NHL, with or without transformation, who were relapsed/refractory (rel/ref) to chemotherapy. The response rates in these 4 studies ranged from 47% to 64%, with median durations of response ranging from 12 to 18 months. **Methods:** The goal of the study was to determine the number of patients who achieved long-term durable complete responses (CR) in both the rituximab-rel/ref group and the rituximab-naive group and to assess their durations of response. A durable CR was defined as a CR with a progression-free survival (PFS) of ≥ 12 months as assessed by a blinded, independent panel of oncologists and radiologists (MIRROR Panel). **Results:** Of the 230 patients evaluable for response, 55 (24%) met the definition of a durable CR (11 of 40 [28%] from the rituximab-rel/ref study, and 44 of 190 [23%] from the 4 studies in rituximab-naive patients).

Patient Demographics for Durable Complete Responders

	Rituximab naive patients	Rituximab rel/ref patients
Median age years, (range)	52 (23-82)	53 (39-73)
Stage III/IV at study entry, %	93	73
Transformed histology, %	27	9
Mean prior therapies, n	3.1	4.1
Prior radiotherapy, %	18	27
Maximum tumor diameter ≥ 5 cm, %	44	18
Median follow-up, years (range)	5.0 (1.3-9.5)	3.9 (3.0-4.6)

Among rituximab-naive patients, median duration of response was 4.9 years. Among rituximab-rel/ref patients, median duration of response has not been reached, with a median follow-up of 3.9 years. Thirty-three of 44 (75%) patients with durable CRs in the rituximab-naive population continue in CR at their last assessment. Eight of 11 (73%) patients with durable CRs in the rituximab-rel/ref group continue in CR at their last assessment. **Conclusions:** Independently assessed durable CRs were noted with similar frequency in patients with rituximab-rel/ref disease (28%) and rituximab-naive patients with chemotherapy-rel/ref disease (23%). With a median follow-up of 4.6 years, 75% of patients with durable CRs continue in complete remission. The BEXXAR therapeutic regimen produced durable CRs in patients with follicular NHL who had relapsed following rituximab or who were refractory to rituximab, and in patients who had never received rituximab.
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Sunday, December 7, 2003 4:15 PM

Simultaneous Session: Chemotherapy/Rituximab Combinations and Radioimmunotherapy (4:15 PM-5:45 PM)

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Treatment With Ibritumomab Tiuxetan Radioimmunotherapy in Patients With Rituximab-Refractory Follicular Non-Hodgkin's Lymphoma

By Thomas E. Witzig, Ian W. Flinn, Leo I. Gordon, Christos Emmanouilides, Myron S. Czuczman, Mansoor N. Saleh, Larry Cripe, Gregory Wiseman, Teresa Olejnik, Pratik S. Multani, and Christine A. White

Purpose: **Rituximab is commonly used as a single agent or in combination therapy for non-Hodgkin's lymphoma (NHL). Ibritumomab tiuxetan radioimmunotherapy targets the same antigen as rituximab and has demonstrated efficacy in rituximab-naïve NHL. This study evaluated ibritumomab tiuxetan in the treatment of rituximab-refractory follicular NHL.**

Patients and Methods: **Eligible patients were refractory to rituximab; this was defined as no objective response to rituximab (375 mg/m² weekly for 4 weeks) or time to progression (TTP) of ≤ 6 months. The ibritumomab tiuxetan treatment regimen consisted of pretreatment with rituximab (250 mg/m² intravenously on days 1 and 8) to deplete peripheral blood B cells, then yttrium-90 ibritumomab tiuxetan (0.4 mCi/kg; maximum, 32 mCi) intravenously on day 8, administered on an outpatient basis. An imaging/dosimetry dose of indium-111 ibritumomab tiuxetan (5 mCi) was injected after rituximab (day 1) in 28 patients.**

Results: **Fifty-seven patients were treated. The median age was 54 years, 74% had tumors ≥ 5 cm, and all were extensively pretreated (median, four prior therapies; range, one to nine). The estimated radiation-absorbed doses to healthy organs were below the study-defined limit in all patients studied with dosimetry. The overall response rate for the 54 patients with follicular NHL was 74% (15% complete responses and 59% partial responses). The Kaplan-Meier–estimated TTP was 6.8 months (range, 1.1 to ≥ 25.9 months) for all patients and 8.7 months for responders. Adverse events were primarily hematologic; the incidence of grade 4 neutropenia, thrombocytopenia, and anemia was 35%, 9%, and 4%, respectively.**

Conclusion: **Ibritumomab tiuxetan radioimmunotherapy is effective in rituximab-refractory patients. The only significant toxicity is hematologic.**

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RITUXIMAB (RITUXAN; IDEC Pharmaceuticals, San Diego, CA, and Genentech, Inc, South San Francisco, CA) is a chimeric anti-CD20 monoclonal antibody that was approved in 1997 by the United States Food and Drug Administration for the treatment of relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL). A 48% overall response rate (ORR) and a time to progression (TTP) of approximately 1 year were demonstrated in the pivotal trial of rituximab.[1] Recent studies have indicated that responses can be reinduced on retreatment with rituximab[2] and that rituximab can be used concomitantly with chemotherapy.[3-6]

Technical advances have made it possible to link radionuclides such as yttrium-90 (^{90}Y) to monoclonal antibodies specifically to target radiation to lymphoma cells. Yttrium-90 is a beta-emitting radionuclide that delivers 90% of its radiation (2.3 MeV) over a mean path length of 5 mm and has a half-life of 64 hours. These characteristics are particularly advantageous for treating bulky, poorly vascularized tumors and those with heterogeneous antigen expression.

Ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals) is a short-course radioimmunotherapy that uses immunobiologic and radiolytic mechanisms of action to destroy both dividing and nondividing tumor cells. Ibritumomab is the murine, parent anti-CD20 antibody that was engineered to develop rituximab. Tiuxetan is a linker/chelator covalently attached to ibritumomab. Ibritumomab tiuxetan can chelate indium-111 (^{111}In) for imaging or ^{90}Y for therapy. Thus, the antibody specifically targets radiation to CD20$^+$ cells while sparing normal nonlymphoid cells.

Because rituximab immunotherapy is widely used to treat patients with NHL, a critical issue is whether patients treated previously with rituximab can respond to ibritumomab tiuxetan. This study tested the hypothesis that tumor resistance to an unconjugated anti-CD20 antibody alone can be overcome by subsequent CD20-directed radioimmunotherapy.

PATIENTS AND METHODS

Eligibility

Eligible patients with follicular B-cell NHL had prior treatment with rituximab, 375 mg/m² once weekly for 4 weeks, and either did not

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respond or had a TTP of less than 6 months. The follicular NHL histologic subtype (Revised European-American Lymphoma classification,[7] follicle center grade 1, 2, or 3) was confirmed by biopsy. The study prospectively allowed enrollment of patients with small lymphocytic or transformed NHL who were rituximab nonresponders from the control arm of a randomized ibritumomab tiuxetan trial,[8] although such patients were to be included in the analysis of safety only.

Patients were to be at least 18 years old and have bidimensionally measurable disease with at least one lesion measuring ≥ 2.0 cm in a single dimension, less than 25% bone marrow involvement with lymphoma, World Health Organization performance status ≤ 2, absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3, platelet count ≥ 150,000 cells/mm^3, serum creatinine and total bilirubin ≤ 2 mg/dL each, expected survival ≥ 3 months, no antineoplastic therapy for 3 weeks (6 weeks if treated with nitrosourea or mitomycin), and no hematopoietic growth factor treatment (granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) within 2 weeks of study entry. Patients with prior autologous bone marrow transplantation or peripheral blood stem-cell support, prior radioimmunotherapy, or external-beam radiation therapy to more than 25% of active bone marrow were not eligible. Also, patients were to have no measurable serum human antimurine or antichimeric antibodies (HAMA or HACA, respectively). Patients were required to sign written, informed consent, and each clinical site had to obtain institutional review board approval before conducting this study.

Study Design

Patients were to receive one course of standard ibritumomab tiuxetan outpatient treatment, as described previously[9]; no hospitalization, patient isolation, or shielding was required. Briefly, this consisted of an infusion of rituximab 250 mg/m^2 on day 1 and day 8 (range, days 7 to 9) and ^{90}Y ibritumomab tiuxetan (0.4 mCi/kg [15 MBq/kg]; maximum, 32 mCi [1.2 GBq]) on day 8 (range, days 7 to 9) immediately after the second rituximab infusion. Radioincorporation of ^{90}Y or ^{111}In into the immunoconjugate was to be performed at each clinical site or at an affiliated commercial radiopharmacy. Acceptable radioincorporation was to be ≥ 95% for both ^{90}Y and ^{111}In radionuclides, as determined with an instant thin-layer chromatographic method.[10,11]

Radiation dosimetry, performed as defined prospectively in the protocol, was to include an imaging/dosimetry dose of ^{111}In ibritumomab tiuxetan (5 mCi; 185 MBq) to be administered immediately after the rituximab infusion on day 1. Dosimetry was to be performed at the clinical site to ensure that no patient received an estimated radiation-absorbed dose greater than 20 Gy to healthy organs and greater than 3 Gy to red marrow. The protocol was amended during enrollment to remove the dosimetry requirement.

For the purpose of collecting safety data, a treatment period was defined as the time from the rituximab infusion on day 1 to 12 weeks after ^{90}Y ibritumomab tiuxetan. Disease status evaluations included a combination of medical history, physical examination, bone marrow biopsy, and computed tomography scan or magnetic resonance imaging of the neck, chest, abdomen, and pelvis, as well as other clinically relevant information. Before treatment, lesions were measured bidimensionally, and the sum of the products of the longest perpendicular diameters (SPD) was calculated as a reference to determine baseline disease status. Posttreatment follow-up evaluations were to be conducted at 1 month and then at 3-month intervals for the first 2 years, and at 6-month intervals for the next 2 years or until disease progression. Safety follow-up continued until disease progression necessitated intervention with another antineoplastic therapy. Efficacy (intent to treat) was to be evaluated in patients with follicular histology only, whereas safety analyses (intent to treat) were to include all enrolled patients.

Patients were evaluated for response by an independent, third-party panel of radiologists and oncologists who were expert in lymphoma (Lymphoma Experts Confirmation of Response). The panel was blinded to the investigator's response assessment. Response was classified according to protocol-defined criteria and International Workshop NHL response criteria.[12] Response is reported here by using International Workshop NHL response criteria, because those are now the accepted standards.

Statistical Methods

The primary efficacy end point was a target ORR (complete response [CR] plus continuous complete remission plus partial response [PR]) of at least 35% in patients with follicular NHL as assessed by Lymphoma Experts Confirmation of Response. Secondary efficacy end points included TTP and duration of response (DR). TTP was defined as the time from the date of the first infusion given on day 1 in this study to the date of disease progression; DR was calculated from the date of the first response observation to the date of disease progression. Time-to-event variables were estimated with the Kaplan-Meier product-limits method.[13]

An additional secondary efficacy end point prospectively defined in the protocol was the comparison of the ORR and DR with the ORR and DR obtained with the prior rituximab therapy and with the last prior chemotherapy, by using McNemar's test. A second exploratory analysis comparing ibritumomab tiuxetan with prior chemotherapy and prior rituximab therapy by using the sign test and signed-rank test was performed at the request of the Food and Drug Administration. The analysis was defined in the following manner: (1) ibritumomab tiuxetan was favored if a patient responded to ibritumomab tiuxetan but not to rituximab (or chemotherapy), and if a patient responded to both, the DR to ibritumomab tiuxetan must have been ≥ 3 months longer than the response to the prior therapy; (2) rituximab (or chemotherapy) was favored if a patient responded to rituximab (or chemotherapy) but not to ibritumomab tiuxetan, and if a patient responded to both, the DR to rituximab (or chemotherapy) must have been ≥ 3 months longer than the response to ibritumomab tiuxetan; and (3) the response was classified as neutral if a patient did not respond to either therapy or responded to both but the DR to ibritumomab tiuxetan was within 3 months of the DR to both.

The patients' perceived quality of life was assessed with a self-rating instrument, the Functional Assessment of Cancer Therapy–General questionnaire,[14] at baseline and at 12 weeks after treatment. Differences in the total score were evaluated with the paired *t* test.

Safety assessments were based on analysis of adverse events and clinical laboratory data by using the National Cancer Institute adult toxicity criteria, version 2.0. Laboratory assessments included hematology and blood chemistry data, serum HAMA/HACA, and monitoring of peripheral blood lymphocyte subpopulations with flow cytometry (B cells were defined as those expressing the CD19 cell-surface antigen). The duration of hematologic toxicity for each hematologic variable (ANC, platelet count, and hemoglobin concentration) was calculated by using two methods. In method A, duration was measured from the date of the last laboratory value before the development of grade 3 or 4 toxicity to the date of the next value in grade 2 after the nadir. In method B, duration was measured from the date of the first laboratory value in grade 3 or 4 toxicity to the date of the last value in grade 3 after the nadir. Baseline residual serum rituximab concentrations were measured before the rituximab infusion on day 1.

An exploratory analysis was conducted to determine whether a relationship existed between a patient's baseline bone marrow involve-

ment with NHL as determined by light microscopy and grade 4 hematologic toxicity after treatment with ibritumomab tiuxetan. Patients were sorted into four groups on the basis of bone marrow involvement: 0% bone marrow involvement, 0.1% to 5.0% bone marrow involvement, 5.1% to less than 20% bone marrow involvement, and ≥ 20% bone marrow involvement. *P* values were generated by Fisher's exact two-tailed test.

RESULTS

Patient Characteristics

Fifty-seven patients were enrolled and completed treatment at 18 clinical sites between July 7, 1998, and October 12, 1999. Patient characteristics are listed in Table 1. Fifty-four patients had follicular NHL (grade 1, 28 patients [52%]; grade 2, 21 patients [39%]; and grade 3, five patients [9%]), two patients had small lymphocytic NHL, and one had transformed diffuse large-cell NHL. Patients were extensively pretreated, and 74% had tumors ≥ 5 cm.

Dosimetry

^{111}In ibritumomab tiuxetan imaging and dosimetry were performed in 28 patients, and the complete results were reported separately.[15] The estimated radiation-absorbed doses were within acceptable levels, allowable for proceeding with ^{90}Y ibritumomab tiuxetan treatment in all patients. The median estimated radiation-absorbed doses were 8.1 Gy to the spleen (range, 4.2 to 23.0 Gy); 5.1 Gy to the liver (range, 2.6 to 12.0 Gy); 2.0 Gy to the lungs (range, 1.4 to 5.3 Gy); 0.22 Gy to the kidneys (range, < 0.01 to 0.66 Gy); and 0.74 Gy to red marrow (range, 0.29 to 1.2 Gy).

Efficacy

The ORR was 74% (40 of 54 patients), with 15% (eight of 54) CRs and 59% (32 of 54) PRs. Ibritumomab tiuxetan produced a tumor shrinkage (reduction in the SPD) in 94% (51 of 54) of patients. The mean reduction in SPD was 74% in the 32 patients who achieved a PR and was 34% in the 14 patients with stable disease.

The ORR to ibritumomab tiuxetan therapy was not statistically different ($P < .05$) in patients with or without bone marrow involvement (81% *v* 71%), in those with or without splenomegaly (83% *v* 73%), and in patients weighing ≤ 80 kg who were dosed per kilogram or patients weighing more than 80 kg who received a capped dose of 32 mCi (77% *v* 68%). Half of patients with bulky disease more than 10 cm and 68% who received four or more prior antineoplastic regimens responded to ibritumomab tiuxetan. No statistically significant difference was found between the response of patients with measurable serum rituximab concentrations (66%; 25 of 38) and those with undetectable serum rituximab concentrations (93%; 13 of 14 [$P = .078$]), although a trend was demonstrated. Peripheral blood B cells were quantitated at baseline by using flow cytometry in all 54 patients with follicular NHL. Forty-seven percent (nine of 19 patients) with no detectable B cells responded to ibritumomab tiuxetan compared with 88% (29 of 33) with measurable B cells ($P = .003$).

Table 1. Patient Characteristics (N = 57)

Characteristic	No.	%
Lymphoma histology		
Follicular	54	95
Small lymphocytic	2	4
Transformed large-cell	1	2
Age, years		
Median	54	
Range	34-73	
Female	29	51
White	54	95
Disease stage at study entry		
I/II	6	10
III/IV	51	90
Tumor size		
< 5 cm	15	26
5 to < 7 cm	17	30
7 to < 10 cm	14	25
≥ 10 cm	11	19
Splenomegaly	7	12
Bone marrow involvement	18	32
Two or more extranodal disease sites	10	18
WHO performance status		
0, 1	54	95
2	3	5
IPI risk group (if known)		
Low	25	44
Low/intermediate	12	21
Intermediate/high	7	12
High	4	7
B-cell count in peripheral blood		
Undetectable	21	37
Low (< 32 cells/mm^3)	20	35
Normal/high (≥ 32 cells/mm^3)	14	25
Unknown	2	4
Median no. of prior antineoplastic therapy regimens	4 (1-9)	
Resistance to chemotherapy*		
Last therapy	37	67
Any therapy	45	82
Prior serum rituximab concentration†		
Undetectable	15	26
1 to < 10 μg/mL	30	53
≥ 10 μg/mL	9	16
Unknown	3	5

Abbreviations: WHO, World Health Organization; IPI, International Prognostic Index.

*Resistance: nonresponders or patients who had disease progression within 6 months.

†Measured before rituximab infusion on day 1.

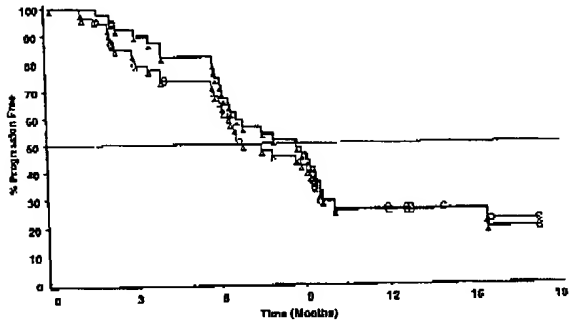

Fig 1. Kaplan-Meier analysis of time to progression for patients with follicular histology: (Δ) intent-to-treat patients, n = 54; (▲) responders, n = 40. C, censored (30%).

The median TTP estimated by the Kaplan-Meier method was 6.8 months (range, 1.1 to ≥ 25.9 months) with 30% of the data censored (Fig 1). The median TTP in the 40 responders was 8.7 months (range, 1.7 to ≥ 25.9 months), with 28% of the data censored. The median DR estimated by the Kaplan-Meier method was 6.4 months (range, 0.5 to ≥ 24.9 months).

Figure 2 displays the ORR achieved with ibritumomab tiuxetan compared with that achieved with prior rituximab and the last chemotherapy. Of the 17 patients who responded to prior rituximab treatment, 88% (15 of 17) responded to ibritumomab tiuxetan, and of the 34 patients who responded to the last chemotherapy, 82% (28 of 34) responded to ibritumomab tiuxetan. In the patients who

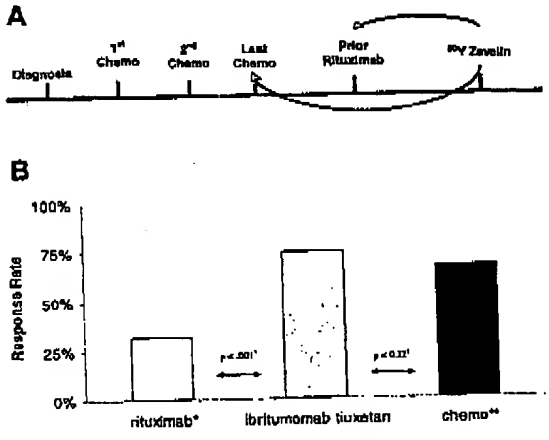

Fig 2. (A) Ibritumomab tiuxetan was the median fifth regimen; chemotherapy was the median third regimen treatment. (B) Comparison of ibritumomab tiuxetan with last prior chemotherapy and prior rituximab.

responded to prior rituximab treatment, the median DR was 11.5 months for ibritumomab tiuxetan (46% of patients censored) and 3.0 months for rituximab (no patient censored; $P = .001$). In the 25 patients in whom DR information was available for the last chemotherapy, the median DR was 5.4 months for ibritumomab tiuxetan (16% of patients censored) and 5.0 months for last chemotherapy (no patient censored; $P = .76$). Table 2 displays this comparison based on response to treatment and DR in a combined analysis as described in the Patients and Methods, under Statistical Methods.

Functional Assessment of Cancer Therapy–General quality-of-life survey data were available for 20 patients. The mean score of 85 before ibritumomab tiuxetan treatment improved significantly to 92.8 at 12 weeks after treatment ($P = .003$). Disease-related symptoms improved or resolved in all responders.

Safety

Adverse events after ibritumomab tiuxetan treatment were primarily hematologic and transient; no patient discontinued treatment because of an adverse event. The duration of hematologic toxicity is listed in Table 3.

The incidence of grade 4 neutropenia, thrombocytopenia, and anemia was 35%, 9%, and 4%, respectively. With Fisher's exact two-tailed test, as described under Statistical Methods, the incidence of the grade 4 ANC nadir correlated statistically with increasing bone marrow involvement with NHL ($P = .004$). In particular, 28% of patients with no bone marrow involvement developed grade 4 ANC nadirs, whereas 100% of patients with 20% to 25% bone marrow involvement developed grade 4 ANC nadirs. No statistically significant difference in grade 4 hematologic toxicity was observed between patients weighing ≤ 80 kg and patients weighing more than 80 kg ($P = .526$ to $.999$ for hemoglobin, ANC, and platelets). No correlation existed between hematologic nadirs and either baseline serum rituximab concentrations or baseline peripheral blood B-cell counts. Eighteen patients (32%) received growth factor therapy: 11 (19%) received erythropoietin, five (9%) received granulocyte colony-stimulating factors, and one (2%) received a platelet growth factor. Thirteen patients (23%) received platelet transfusions, and 14 (25%) received RBC transfusions.

The most common nonhematologic events during the treatment period were infusion related (Table 4) and were consistent with those described for rituximab infusion.[1] These included asthenia in 54% (31 of 57 patients), nausea in 35% (20 of 57), chills in 25% (14 of 57), and fever in 21% (12 of 57). Eighty-three adverse events occurred on a treatment day (66 on day 1 and 22 on day 8); all were grade 1 or 2 except one (grade 3 tumor pain). Four patients (7%) were hospitalized, one each with febrile neutropenia, pneu-

Table 2. Additional Comparison of Ibritumomab Tiuxetan Versus Prior Rituximab Therapy or Last Chemotherapy (n = 54)*

Variable	Favors,† (%)		Neutral (%)	P	
	Ibritumomab Tiuxetan	Prior Therapy		Signed-Rank Test	Sign Test
Ibritumomab tiuxetan versus prior rituximab	48	9	43	< .001	.011
Ibritumomab tiuxetan versus last chemotherapy*	30	30	41	.388	.377

*Ibritumomab tiuxetan was the median fifth regimen; chemotherapy was the median third-regimen treatment.

†Defined as (1) response to one therapy but not to the other, or if response to both, the DR must be ≥ 3 months longer than response to the other therapy; (2) neutral if a patient did not respond to either therapy or responded to both but the DR to ibritumomab tiuxetan was within 3 months of the DR to both (see Patients and Methods).

monia/sepsis, cellulitis, and urinary tract infection. No patient developed HACA, and one patient developed a low-titer HAMA (29 μg/mL) on day 42. This patient experienced no adverse events attributable to HAMA and achieved a PR. One patient with a detectable HACA titer at study entry (44.7 ng/mL) received an exemption to allow treatment. This patient did not respond to ibritumomab tiuxetan and experienced no grade 3 or 4 or other serious adverse event.

One patient died as a result of acute myelogenous leukemia (AML) approximately 14 months after treatment. The patient had previously received single-agent and combination chemotherapy, including chlorambucil; cyclophosphamide, doxorubicin, vincristine, and prednisone; and prednisone, methotrexate, doxorubicin, cyclophosphamide, and etoposide/mechlorethamine, vincristine, procarbazine, and prednisone. Blasts were detected in the patient's peripheral blood during the first month after ibritumomab tiuxetan treatment. AML was diagnosed at month 8, when cytogenetic studies demonstrated monosomy 7, inversion 3q, and t(21;22). Subsequent analysis of pretreatment bone marrow for this patient revealed 23% of cells with monosomy 7; however, this was within the normal range for the assay (upper normal limit, 25%). One patient taking oral anticoagulant therapy for a history of deep vein thrombophlebitis and self-prescribed ibuprofen died on study day 71 as a result of a traumatic subdural hematoma that occurred at platelet nadir.

DISCUSSION

Patients with advanced-stage follicular NHL are likely to die as a result of that disease.[16] Most patients respond to subsequent treatments; however, recurrence, progression, transformation to a more aggressive histology, or a combination of these is typically unavoidable.[17] Patients usually have repeated relapses, and subsequent courses of chemotherapy characteristically lead to fewer and shorter remissions.[18] Cumulative toxicity associated with cytotoxic chemotherapy often necessitates dose reduction, shorter courses, or drug substitutions, each of which may compromise response to treatment. Rituximab immunotherapy has been an important treatment advance in NHL because of its efficacy, short duration of therapy, and acceptable toxicity profile. The aim of this study was to evaluate whether rituximab-refractory patients could achieve responses with an anti-CD20 radioimmunotherapy directed against the same epitope as rituximab.

Fifty-four patients with rituximab-refractory follicular NHL received the ibritumomab tiuxetan regimen and achieved a 74% ORR (15% CR). This response rate exceeded the protocol-targeted 35% ORR and is particularly encouraging in this patient population, which was extensively pretreated (median of four regimens) with chemotherapy. By using two separate analysis methods, ibritumomab tiuxetan efficacy was superior to prior rituximab therapy and compared favorably with last chemotherapy.

Table 3. Duration of Hematologic Toxicity

Variable	Baseline	Nadir	Days From Baseline to Nadir	Median Duration for Patients With Grade 3 or 4 Nadir (days)*	
				Method A	Method B
ANC, cells/mm³	3,500	700	63	22	8
Platelets, cells/mm³	214,000	33,000	55	24	12
Hemoglobin, g/dL	13.3	9.9	68	8	1

*ANC < 1,000 cells/mm³; platelets < 50,000 cells/mm³; and hemoglobin < 8 g/dL. Method A, duration measured from the last date in grade 2 before nadir to the first date in grade 2 after nadir; method B, duration measured from the first date in grade 3 or 4 before nadir to the last date in grade 3 or 4 after nadir.

Table 4. Incidence of Most Common and Grade 3 or 4 Nonhematologic Adverse Events (N = 57)*

Event	Grade 1	Grade 2	Grade 3	Grade 4	Total No.	Total %
Body as a whole						
Asthenia	17	12	2	0	31	54
Chills	12	2	0	0	14	25
Fever	5	6	1	0	12	21
Headache	4	3	0	0	7	12
Throat irritation	6	1	0	0	7	12
Abdominal pain	3	4	0	0	7	12
Neck pain	1	0	1	0	2	4
Tumor pain	0	0	1	0	1	2
Sepsis	0	0	0	1	1	2
Cardiovascular system						
Deep vein thrombophlebitis	0	0	1	0	1	2
Digestive system						
Nausea	17	3	0	0	20	35
Pancytopenia	0	0	0	1	1	2
Respiratory system						
Dyspnea	6	1	0	0	7	12
Pneumonia	0	0	0	1	1	2
Urogenital system						
Vaginal hemorrhage	0	0	1	0	1	2

*The incidence was ≥ 10% of patients and all grade 3 or 4 adverse events that occurred during the treatment period and classified as probably or possibly related to study drug or relationship unknown. Each patient was counted only once under the worst-grade adverse event experienced, excluding neutropenia, leukopenia, thrombocytopenia, and anemia.

The myelosuppression associated with ibritumomab tiuxetan is gradual in onset and occurs later than typical chemotherapy-induced myelosuppression. Despite myelosuppression, infections were unusual; only 7% of patients were hospitalized, and there were no infection-related deaths. The correlation between percentage of bone marrow involvement with lymphoma and hematologic toxicity confirmed that hematologic toxicity was related to specific targeting of ^{90}Y ibritumomab tiuxetan to marrow and secondary irradiation of marrow hematopoietic cells. The majority of nonhematologic events consisted of grade 1 or 2 constitutional symptoms such as asthenia, nausea, fever, and chills associated with infusion days. Similarly, the most common grade 3 or 4 nonhematologic events were asthenia and pain and were experienced by only 11% of patients.

One patient developed AML and died approximately 14 months after ibritumomab tiuxetan treatment. Baseline marrow cytogenetic data revealed possible pretreatment chromosomal abnormalities, and blasts were apparent in the patient's peripheral blood as early as the first month of the study, suggesting that the condition was incipient. Secondary AML has been observed with increasing frequency among NHL patients, and the contribution of prior alkylator therapy seems unequivocal.[19-23] Moreover, the possibility that certain NHL patients are prone to the development of secondary AML has not been ruled out.[19] It will be important to observe patients carefully for the development of late marrow toxicity.

A primary concern of re-treatment with monoclonal antibody-based therapy is the development of antixenogenic antibodies (HAMA and HACA) that may reduce the therapeutic antibody serum half-life and increase the risk of adverse events such as fever, hypotension, rash, arthritis and arthralgias, and nerve palsies.[24-26] However, only one patient (< 2%) developed HAMA in this study, and this patient achieved a PR. This low incidence of HAMA and HACA responses is consistent with findings in other ibritumomab tiuxetan trials.[9,27-29] One additional patient with a HACA titer at baseline experienced no unusual toxicity or adverse events after treatment with ibritumomab tiuxetan.

Some patients had received rituximab shortly before entering this study. Prior treatment with rituximab did not compromise patient safety; all normal organ doses were acceptable and were consistent with those observed in other ibritumomab tiuxetan studies.[30,31] The presence of residual serum rituximab or the absence of peripheral blood B cells at baseline did not preclude tumor response, although response rates tended to be lower for patients with these factors. As demonstrated previously for both rituximab-refractory and rituximab-naïve patients, undetectable B cells at baseline predicted a shorter disease-free interval and poor prognosis.[32] However, no measurable difference in

hematologic toxicity was noted in patients stratified by either residual serum rituximab concentration or baseline peripheral blood B-cell count as measured by grade 4 ANC, platelet, and hemoglobin nadir values. Therefore, it seems that the trend toward lower response rates is not due to altered biodistribution, but that these unfavorable baseline factors select for a poorer-prognosis population. Patients with these factors may nevertheless achieve a favorable tumor response.

This study demonstrates that patients can be safely and effectively treated with ibritumomab tiuxetan after prior treatment with rituximab. The challenge in future studies will be to evaluate whether high-dose therapy with stem-cell support or combined-modality therapy with chemotherapy will enhance the CR rate and TTP in this patient population. In addition, trials should be undertaken to evaluate whether the effect of ibritumomab tiuxetan can be enhanced by the addition of cytokines or unlabeled monoclonal antibodies, since Ansell et al[23] recently demonstrated a 69% ORR in a phase I trial of rituximab and interleukin-12.

Initial trials of single-dose anti-CD20 radioimmunoconjugates have clearly demonstrated efficacy in producing tumor responses. In addition, high scores have been obtained in measures of patient satisfaction with treatment and for quality of life. The current challenge is to optimize the integration of ibritumomab tiuxetan radioimmunotherapy into the treatment paradigm of B-cell NHL to maximize both tumor response and patient safety.

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The acknowledgment is available online at www.jco.org.

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EDITORIALS

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BEXXAR®

Tositumomab and Iodine I 131 Tositumomab

WARNINGS

Hypersensitivity Reactions, including Anaphylaxis: Medications for the treatment of severe hypersensitivity reactions should be available for immediate use. Patients who develop severe hypersensitivity reactions should have infusions of the BEXXAR therapeutic regimen discontinued and receive medical attention (See **WARNINGS**).

Prolonged and Severe Cytopenias: The majority of patients who received the BEXXAR therapeutic regimen experienced severe thrombocytopenia and neutropenia. The BEXXAR therapeutic regimen should not be administered to patients with >25% lymphoma marrow involvement and/or impaired bone marrow reserve (See **WARNINGS** and **ADVERSE REACTIONS**).

Pregnancy Category X: The BEXXAR therapeutic regimen can cause fetal harm when administered to a pregnant woman.

Special requirements: The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) contains a radioactive component and should be administered only by physicians and other health care professionals qualified by training in the safe use and handling of therapeutic radionuclides. The BEXXAR therapeutic regimen should be administered only by physicians who are in the process of being or have been certified by Corixa Corporation in dose calculation and administration of the BEXXAR therapeutic regimen.

DESCRIPTION

The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) is an anti-neoplastic radioimmunotherapeutic monoclonal

antibody-based regimen composed of the monoclonal antibody, Tositumomab, and the radiolabeled monoclonal antibody, Iodine I 131 Tositumomab.

Tositumomab

Tositumomab is a murine IgG_{2a} lambda monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Tositumomab is produced in an antibiotic-free culture of mammalian cells and is composed of two murine gamma 2a heavy chains of 451 amino acids each and two lambda light chains of 220 amino acids each. The approximate molecular weight of Tositumomab is 150 kD.

Tositumomab is supplied as a sterile, pyrogen-free, clear to opalescent, colorless to slightly yellow, preservative-free liquid concentrate. It is supplied at a nominal concentration of 14 mg/mL Tositumomab in 35 mg and 225 mg single-use vials. The formulation contains 10% (w/v) maltose, 145 mM sodium chloride, 10 mM phosphate, and Water for Injection, USP. The pH is approximately 7.2.

Iodine I 131 Tositumomab

Iodine I 131 Tositumomab is a radio-iodinated derivative of Tositumomab that has been covalently linked to Iodine-131. Unbound radio-iodine and other reactants have been removed by chromatographic purification steps. Iodine I 131 Tositumomab is supplied as a sterile, clear, preservative-free liquid for IV administration. The dosimetric dosage form is supplied at nominal protein and activity concentrations of 0.1 mg/mL and 0.61 mCi/mL (at date of calibration), respectively. The therapeutic dosage form is supplied at nominal protein and activity concentrations of 1.1 mg/mL and 5.6 mCi/mL (at date of calibration), respectively. The formulation for the dosimetric and the therapeutic dosage forms contains 5.0%–6.0% (w/v) povidone, 1–2 mg/mL maltose (dosimetric dose) or 9–15 mg/mL maltose (therapeutic dose), 0.85–0.95 mg/mL sodium chloride, and 0.9–1.3 mg/mL ascorbic acid. The pH is approximately 7.0.

1: Int J Oncol. 1999 Nov;15(5):1017-25. Related Articles, Link

Preclinical evaluation of 90Y-labeled anti-CD20 monoclonal antibody for treatment of non-Hodgkin's lymphoma.

Chinn PC, Leonard JE, Rosenberg J, Hanna N, Anderson DR.

IDEC Pharmaceuticals Inc., San Diego, CA 92121, USA.

A high-affinity IgG1 kappa murine monoclonal anti-CD20 antibody (IDEC-2B8) was developed for radioimmunotherapy of non-Hodgkin's B-cell lymphoma. A stable immunoconjugate (Zevalintrade mark) was prepared by reacting IDEC-2B8 with a derivative of diethylenetriaminepentaacetic acid, designated MX-DTPA, a chelator exhibiting high affinity and retention for 90Y. Zevalin exhibited antigen specificity, human tissue reactivity, and preclinical safety profile comparable to the native antibody. The conjugate radiolabeled with 90Y (90Y-Zevalin) or 111In (111In-Zevalin) exhibited excellent retention of immunoreactivity with radioincorporations >95%. The radiolabeled conjugates formulated in PBS containing human serum albumin were stable in vitro at 4 degrees C for 48 h as indicated by negligible loss of radioisotope and retention of binding to CD20+ cells. In vitro human serum stability studies at 37 degrees C with 90Y-Zevalin indicated that loss of 90Y from the conjugate was minimal, averaging 1% per day. Biodistribution studies in BALB/c mice confirmed the in vitro stability of 90Y-Zevalin and 111In-Zevalin. In particular, excellent in vivo retention of 90Y by the conjugate was demonstrated by minimal bone accumulation (</=3% of the injected dose over three days). Radiation dose estimates to normal organs calculated from mouse biodistribution studies with 90Y-Zevalin were comparable to those determined in a phase I/II clinical trial and below generally accepted safe radiation levels. Studies in athymic mice bearing CD20+ tumors demonstrated that 111In-Zevalin accumulated in the tumors preferentially compared with normal organs. 90Y-Zevalin is currently being evaluated in phase III clinical trials for treatment of relapsed or refractory low-grade, follicular or transformed B-cell non-Hodgkin's lymphoma.

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